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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/657,550
Filing Date: September 04, 2003
Appellant(s): CHAUDRY, IMTIAZ

Mr. John E. Johnson, III
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed June 10, 2011 appealing from the Office action mailed August 6, 2010.

(1) Real Party in Interest

The examiner has no comment on the statement, or lack of statement, identifying by name the real party in interest in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The following is a list of claims that are rejected and pending in the application:

Claims 1, 4-6, 10-12, 22-25, 27-30, 35, 71-77 are pending and all these claims are rejected.

(4) Status of Amendments After Final

The examiner has no comment on the appellant's statement of the status of amendments after final rejection contained in the brief.

(5) Summary of Claimed Subject Matter

The examiner has no comment on the summary of claimed subject matter contained in the brief.

(6) Grounds of Rejection to be Reviewed on Appeal

The examiner has no comment on the appellant's statement of the grounds of rejection to be reviewed on appeal. Every ground of rejection set forth in the Office action from which the appeal is taken (as modified by any advisory actions) is being maintained by the examiner except for the grounds of rejection (if any) listed under the subheading "WITHDRAWN REJECTIONS." New grounds of rejection (if any) are provided under the subheading "NEW GROUNDS OF REJECTION."

(7) Claims Appendix

The examiner has no comment on the copy of the appealed claims contained in the Appendix to the appellant's brief.

(8) Evidence Relied Upon

FLONASE® entry from the online Physician's Desk Reference® (PDR®) accessed on December 1, 2007 at www.thomsonhc.com/pdrel/librarian/ND_PR/Pdr/SBK/1/PFPUI/0S1HrZu2aVaNqC/DDAK...

Lacy, C. et al. Drug Information Handbook (DIH), Lexi-Comp, Inc.: Cleveland, 1999, pp. 445-446.

6,464,958	Bernini et al.	10-2002
WO 99/18971	Harris et al.	04-1999
US 2002/0061281	Osbakken et al.	05-2002
6,368,616	Doi	04-2002

6,608,054 Meade et al. 08-2003

Walker, S. "Management of Allergic Rhinitis," Nursing Times, 2003, 99(23), abstract.

Hamuy, R. et al. "Topical Antiviral Agents for Herpes Simplex Virus Infections," Drugs Today, 1998, 34(12), abstract.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Appellant Claims
2. Determining the scope and contents of the prior art.
3. Ascertaining the differences between the prior art and the claims at issue, and resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

(A) Claims 1, 4-6, 10-13, 22-25, 27-30, 35, and 77 are rejected under 35 U.S.C. 103(a) as being unpatentable over FLONASE® from the online Physician's Desk Reference

(PDR®), as evidenced by the 1999-2000 Drug Information Handbook (Lacy, C.; Armstrong, L. L.; Armstrong, L. L.; Goldman, M. P.; Lance, L. L., Lexi-Comp, Inc.: Cleveland, 1999, pp. 445-446) in view of Bernini et al. (U.S. Patent No. 6,464,958), Harris (WO 99/18971) (IDS reference) and Osbakken et al. (US 2002/0061281).

Appellant Claims

Appellant claims an aqueous formulation comprising (a) 0.04% to 0.06% w/w of a suspended steroidal anti-inflammatory that is fluticasone or a pharmaceutically acceptable salt, ester, enol, ether, enol ether, enol ester, acid, or base thereof characterized by the particle size distribution described in claim 1, (b) an antifungal agent (e.g. amphotericin beta), further comprising (c) a preservative, such as benzalkonium chloride (e.g. claims 23-24 and 28), (d) other excipients (e.g. dextrose, carboxymethylcellulose sodium, etc.), and (e) an antibiotic (claims 29-30), wherein the formulation is suitable for administration to the para-nasal mucosa.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

The teachings of FLONASE®, the PDR®, the DIH, ad Osbakken are restated herein below.

FLONASE® is a commercially available nasal spray sold in a metering, atomizing, spray pump containing therein an aqueous suspension of suspended microfine fluticasone propionate (16 g bottle delivering 120 individual 50 microgram doses per actuation; i.e. 0.0375% w/w fluticasone propionate), microcrystalline cellulose, carboxymethylcellulose sodium, dextrose, 0.02% w/w benzalkonium chloride, polysorbate 80, 0.25% w/w phenylethyl alcohol, wherein the

aqueous suspension has a pH between 5 and 7 (PDR printout, pg. 1, "Description section"). The recommended dosage of FLONASE® for adults is 50 micrograms per nostril for a total daily dosage of 200 micrograms. Alternatively, the administration of two 100 microgram doses twice daily is also effective. Adolescents and children 4 years of age and older should begin with 100 microgram dosages (1 spray per nostril per day), but may use 200 micrograms (2 sprays per nostril per day) if not adequately responding (PDR, pg. 7, "Dosage and Administration" section).

The DIH demonstrates that FLONASE® was a commercially available product at least as early as 1999. The DIH also sets forth that neomycin sulfate (pg. 721-722) was a known antibiotic at the time of Appellant's invention and that acyclovir (pgs. 26-28), ganiciclovir (pgs. 463-464), foscarnet (pgs. 454-456), cidofovir (pgs. 225-226), and formivirsen (pgs. 453-454) were all known antiviral agents at the time of Appellant's invention.

Bernini teaches a process for the preparation of suspensions of drug particles for inhalation delivery, providing optimized particle size and distribution. A further aspect of the invention is directed to a process for preparing micronized sterile steroidal formulations by gamma-irradiation (abstract; col. 1, lines 17-27; col. 4, lines 14-25).

Bernini teaches that a number of inhalation formulations have been marketed for some years for the administration of steroidal anti-inflammatory agents for the topical treatment of rhinitis and/or sinusitis. An example of these steroidal anti-inflammatory drugs includes beclomethasone dipropionate (BDP). These formulations can be administered in the form of a finely divided (i.e. micronized powder) suspension in an aqueous phase containing necessary surfactants (i.e. emulsifiers) and/or cosolvents. When intended for administration in the form of

metered dose aerosol sprays, these sprays should also contain a low-boiling propellant (col. 1, lines 8-12, 17-20, and 22-26).

Bernini teaches that in the process of preparing her formulations an aqueous solution, which constituted the carrier optionally, contains wetting agents, surfactants (i.e. emulsifiers), preservatives, stabilizing agents, buffers, and can optionally be sterilized.

Bernini teaches that the degree of solid particle size reduction and the resulting particle size distribution of the formulations produced by her process can be optimized by controlling several variables: (i) the type and size of the interaction chamber; (ii) the operating pressure; and (iii) the processing time and the number of cycles the material passed through. The process effects are also dependent on the physicochemical properties of the ingredients subjected to treatment, however pressure and process times can be modified to achieve the desired results (col. 2, lines 33-43).

Bernini teaches that it would be highly advantageous to provide aqueous suspensions of steroids to be delivered in single unit-dose preparations, because sterility is a requirement in greater demand for pharmaceutical formulations intended for nebulization (col. 4, lines 31-36).

Bernini teaches that BDP micronized formulations when subjected to gamma radiation at 2 to 9 KGy remain chemically stable (col. 5, lines 53-55). Bernini states that the invented method allows for the preparation of sterile micronized BDP suspensions (col. 6, lines 19-21). Other drugs, which can be used in Bernini's formulations and methods, include corticoid steroids, such as fluticasone propionate, and other inhalable anti-inflammatory steroids (col. 1, lines 17-27; col. 4, lines 14-25; claims 1, 2, and 5-6).

Bernini teaches that the BDP starting material used in her process has a particle size of less than 10 microns, preferably less than 5 microns. The formulations for inhalation resulting from her invented process can be used to treat any allergic and/or inflammatory condition of the nose or the lungs (col. 6, lines 33-43).

Harris teaches an aqueous nebulizer suspension formulation of mometasone furoate monohydrate, which also comprises a nonionic surfactant, soluble salt, and optionally a pH buffer (title; abstract; claims 1-15), wherein the suspended solid mometasone particles have an average particle size of less than about 5 microns (claim 14; pg. 4, lines 14-16) or less than about 2 microns (claim 15; page 4, lines 14-17). Mometasone furoate is a well-known anti-inflammatory steroid. Harris teaches that the formulations can be obtained in sterile form by preparation under sterile conditions (pg. 9, lines 17-19) and, alternatively, in lieu of sterilization a preservative may be incorporated into the formulations (pg. 4, lines 21-25). Harris teaches that sterilization by filtration is not feasible for a suspension formulation and that sterilization by gamma radiation or heating induces mometasone degradation (pg. 9, lines 8-15).

Harris teaches that the preferred micronization technique is jet milling and that this technique may be used *to reproducibly obtain desired distributions* of micron and submicron sized particles (pg. 10, lines 5-7).

Harris teaches that inhaled therapeutics are typically used to treat airway disorders, including asthma, infections, and various inflammatory conditions (pg. 1, lines 18-20).

Osbakken teaches pharmaceutical compositions are described that comprise one or more active ingredients including an anti-infective agent, anti-inflammatory agent, and antibiotic combinations or combinations of others of these classes of ingredients, especially compositions

formulated as a solution or suspension in a unit dose for aerosol administration to treat chronic sinusitis (abstract).

Osbakken teaches that sinusitis is an inflammation of the membrane lining one or more paranasal sinuses (i.e. paranasal mucosa), and there are three principle kinds of sinusitis: acute, recurrent acute, and chronic [0004]. Therefore, it is obvious that the term rhinosinusitis encompasses sinusitis as in a genus-species relationship, wherein sinusitis is a species of the genus rhinosinusitis. Species are obvious over the genius.

Osbakken teaches that bacteria commonly associated with acute sinusitis, and that, although less common fungal sinusitis does occur and is often associated with infections caused *by Aspergillus, Vurvularia, Bipolaris, Exserohilum, Metarrhizium anisopliae,* and *Mucormycosis* fungi [0007]-[0008]. The primary objectives for the treatment of sinusitis are reduction of swelling, eradication of infection, draining of the sinuses, and ensuring that the sinuses remain open [0015]. Nebulization therapy is a conventional treatment for pulmonary infections and is also known to have been used for sinus infections, with few systemic side effects [0026].

Osbakken teaches that it had been suggested previously in the prior art to use small aerosol particles of about 2-4 microns in the treatment of sinusitis. See paragraphs [0027]-[0029], especially [0029].

Osbakken teaches that the use of synergistic antibiotic combination is desirable; because it allows for the treatment of more difficult infections (e.g. infections due to multiple-antibiotic-resistant organisms) and lower dosages, thereby reducing the probability of toxicity complications, treatment time, and therapy cost. For example, cefuroxime and gentamicin, either

individually or in combination with other agents, have been used to treat patients with sinusitis [0066]-[0068].

Osbakken teaches that his invention involves the topical delivery of medications to the nasal cavity and sinuses by aerosolizing aqueous solutions or suspensions of the medications taught. The aerosolized anti-infective particles are surprisingly effective when they have a mass median aerodynamic diameter (MMAD) of about 1.0 to 5.0 microns [0081]. Aerosolization/atomization of the formulations for nasal inhalation by a patient will result in liquid aerosol cloud particles having a MMAD of preferably between about 0.5 microns and 10 microns. Examples of suitable medicaments include amphotericin beta (anti-fungal), cefuroxime (antibiotic), ciprofloxacin (antibiotic), tobramycin (antibiotic), cefoperazone (antibiotic), erythromycin (antibiotic), gentamycin (antibiotic) [0085], fluticasone (anti-inflammatory), and beclomethasone (anti-inflammatory) [0139]. An exemplary formulation is described in [0178] and comprises amphotericin beta (10 mg unit dose), hydrocortisone sodium succinate (50 mg dose in 3 ml sterile water) together with an anti-inflammatory agent. Preferable dosage ranges of various active agents including amphotericin beta, beclomethasone, fluticasone, fluconazole, itraconazole, aztreonam, cefepime, doxycycline, tobramycin, vancomycin, etc. are taught in Table-1.

Osbakken teaches that if necessary, osmotic pressure may then be raised to fall within a preferred range by adding NaCl, dextrose, or other salts to the liquid [0096]. Surfactants can be used as dispersing agents, solubilizing agents, and spreading agents. Some examples of surfactants are: PEG 400, sodium lauryl sulfate, spans (20-40-60 etc.), tweens (polysorbates, 20-

40-60 etc.), tyloxapol, propylene glycol, and benzalkonium chloride. Benzalkonium chloride is also a preservative.

Osbakken teaches in [0104] a general preparation of his invented formulations, wherein after determining the medications to be used in the formulation, each ingredient is weighed/measured individually, added together, mixed with diluent (e.g. sterile water), filtered with a coarse filter, and then a fine filter (5 micron, 2 micron, 1 micron, 0.45 micron, or 0.22 micron). The preparation is tested to ensure it is within the established parameters for surface tension, osmolarity, pH, and sodium chloride equivalency. To prepare a unit dose, the ingredients of such formulations generally will be dissolved in a solvent such as water or saline solution, in a volume between about 0.5 and 6.0 ml.

Osbakken teaches a method of treating a mammal suspected or diagnosed as having chronic sinusitis comprising the step of administering to the patient the pharmaceutical composition of any one of claims 1 or 2, by aerosolization using a nebulizer, which delivers aerosol particles of between about 1 to 5 microns in average diameter in claim 16 of US-2002. Osbakken also teaches in [0235] that the medication is nebulized three times daily and that the therapeutic treatment was continued for a total of seven days.

Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)

The product information concerning FLONASE® is silent as to the particle size distribution of suspended beclomethasone. The product size distribution rendered obvious by the teachings of Bernini as further articulated below. FLONASE® lacks the teaching of compositions further comprising an antifungal agent or an antibiotic. This deficiency is cured by

the teachings of Osbakken, which has been provided as a supporting document to show what was known in the art regarding the treatment of rhinitis/sinusitis. Harris is provided as a supporting reference to demonstrate particle sizes recognized in the art as being suitable for nasal administration and that it is conventional to optimize particle size distributions.

Finding of Prima Facie Obviousness Rational and Motivation
(MPEP §2142-2143)

It would have been obvious to a person of ordinary skill in the art at the time of the instant invention to modify the compositions of FLONASE®/Bernini with the teachings of Osbakken, because it was well-known at the time of the instant invention that sinusitis is a species of rhinosinusitis (i.e. rhinitis) and is characterized by inflammation of one or more membranes of the paranasal sinuses (i.e. paranasal mucosae) that can be caused by microbial infection (i.e. fungal or bacterial infection). Using what was readily known to the ordinary skilled artisan at the time of the instant invention, an ordinary skilled artisan would have recognized that the underlying cause of sinusitis or rhinitis could be treated by the inclusion of an anti-microbial agent, such as an anti-fungal agent (e.g. amphotericin beta) or an antibacterial (e.g. doxycycline) in a therapeutically effective dosage. Thus, despite the fact that Osbakken focuses its teachings on aqueous solutions that are filtered, an ordinary skilled artisan would nonetheless have been motivated to modify FLONASE® to incorporate a therapeutically effective amount of an anti-fungal agent and/or an antibacterial to obtain a composition suitable for treating not only the inflammation resulting from an infection, but also suitable for treating the underlying cause of the inflammation (i.e. a fungal and/or bacterial infection). An ordinary skilled artisan would have had a reasonable expectation of success upon modification of the

FLONASE®/Bernini composition to further comprise an anti-fungal or antibacterial agent because these are art-recognized therapeutics for treating fungal and bacterial infections and are known in combination with anti-inflammatory steroids.

Regarding Appellants' data it is clear that the performance of both high and low-dose FLONASE® vis-à-vis the high and low dose formulations of Appellants' invention result in clinically comparable and in some cases indistinguishable results (see for example data points in Appellants' figure 1 at days 7, 10, and 12-14). Appellant has asserted that the claimed particle size distribution results are unexpected. The difference between the low dose and high dose data is that the high dose data is associated with two dosing events of either FLONASE® or Appellant's formulation. It is noted that Appellant's data is limited to formulations comprising 0.050% w/w fluticasone (see Table 3 on page 30 of the specification of copending 10/414,682 incorporated by reference into the instant application).

Appellants' "quantified" subjective data is graphically presented in Figures 1-4 of copending application 10/414,682 which has been considered by the Examiner. It is the Examiner's position that the data presented does not demonstrate unexpected results when compared to the prior art data (FLONASE®). The Appellants' data compared to FLONASE® exhibit the same pattern of fluctuations over a period of 2-14 days; is of a similar magnitude, and in several instances is the same (see, for example, data points at days 4, 5, 9, and 10). It is also noted that the data points are not displayed with error bars. The display of the uncertainty in the data points is deemed necessary because the data reported in Figures 1-4 are based upon a least squares mean analysis of the raw Total Nasal Symptom Scores (TNSS) (*i.e.* these are aggregate data), which are subjective data assigned values by patients on an arbitrary scale of 0 to 3, where

0 means no symptoms and 3 means "severe symptoms present," wherein these subjective data were manipulated using the ANOVA model. For this reason, wherein Appellants' subjective data for the invented compositions and the prior art data points are very similar in magnitude, it would be reasonable for one to conclude that these data points are the same within a margin of error. Furthermore, the general differences depicted in the Figures are merely a difference of degree at best and not a difference of kind. A difference of degree is not sufficient to support patentability. Contrary to Appellant's statements, Appellant's results when taken as a whole and compared to the results exhibited by FLONASE® are not considered to demonstrate anything surprising or unexpected, as has been explained in previously. Thus, Appellant's formulations are not considered to exhibit unexpected or surprising results either.

Regarding the recited particle size distribution, it has already been established that optimization of particle sizes is routine in the field of inhalable formulations (*i.e.* both oral and nasally administered) (Harris). Thus, finding the optimal particle size and particle size distribution for a given particulate formulation is routinely practiced in the art and as applied to the combined prior art, would reasonably be expected to yield the same or a substantially similar particle size distribution as claimed by Appellants.

Regarding the recited stability, Appellant is correct that the combined prior art is silent with regards to the stability as recited in Appellant's claims. However, it is concluded that the recited stability is a consequence of the claimed formulations being sterile, as evidenced by the statements in paragraph [0061] of the PG-PUB of Appellant's specification that the formulation stability may be increased by inclusion of an antimicrobial preservative. The PG-PUB of Appellant's specification at paragraph [0066] indicates that stability of the compositions may be

increased by including an antimicrobial preservative to ensure the sterility of the compositions. Thus, the recited stability appears to be related to the fact that the claimed compositions are sterile and not to the recited particle size distribution or to any particular recited component. Because the prior art teaches the desirability of obtaining sterile formulations (Osbakken and Bernini), it is concluded that the formulations resulting from the combined prior art would necessarily exhibit the recited stability. It is also noted that neither Appellant's specification nor Appellant's arguments correlate the recited stability with the recited particle size distribution. Thus, the above conclusion about the prior art compositions necessarily exhibiting the required stability is reasonable. Appellant is reminded that the Office lacks laboratory facilities to test the sterile prior art compositions to ascertain their stability. Thus, the burden is properly shifted to Appellant to demonstrate that the sterile formulations of the prior art do not exhibit the recited stability. Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because the combined teachings of the prior art is fairly suggestive of the claimed invention. The instant rejection is proper.

(B) Claims 71-74 are rejected under 35 U.S.C. 103(a) as being unpatentable over FLONASE® from the online Physician's Desk Reference (PDR®), as evidenced by the 1999-2000 Drug Information Handbook (Lacy, C.; Armstrong, L. L.; Armstrong, L. L.; Goldman, M. P.; Lance, L. L., Lexi-Comp, Inc.: Cleveland, 1999, pp. 445-446) in view of Bernini et al. (U.S. Patent No. 6,464,958), Harris (WO 99/18971) (IDS reference) and Osbakken et al. (US 2002/0061281), as applied to claims 1, 4-6, 10-13, 22-25, 27-30, and 35

above, and further in view of Doi (U.S. Patent No. 6,368,616) and Meade (U.S. Patent No. 6,608,054).

Appellant Claims

Appellant claims a formulation as described above in the instant application further comprising a complexing agent (e.g. sodium edetate)

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

The teachings of FLONASE®, the PDR®, the DIH, Bernini, Harris, and Osbakken are set forth above.

Doi teaches aqueous suspensions for nasal application and that the compositions may contain additives which are broadly used in nasal drops, such as preservatives, buffers (e.g. citric acid), stabilizers, chelating agents (e.g. citric acid and editic acid), pH control agents (e.g. citric acid), etc. (title; abstract; col. 2, lines 61-65; col. 3, lines 8-17). The term "chelating agent" is synonymous with "complexing agent."

Meade teaches that sodium edetate and citric acid are known complexing agents (col. 9, lines 22-34).

Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)

FLONASE® lacks the teaching of compositions further comprising a complexing agent. This deficiency is cured by the teachings of Doi or Meade, which have been provided as

supporting documents to show that complexing agents are conventional ingredients in aqueous nasal formulations.

Finding of Prima Facie Obviousness Rational and Motivation
(MPEP §2142-2143)

It would have been prima facie obvious to an ordinary skilled artisan at the time of the instant invention to modify the FLONASE®/Bernini/Osbakken compositions to further comprise a conventional additive broadly used in the formulation of nasal compositions, such as complexing agents. Regarding the specific complexing agent used, an ordinary skilled artisan would have been motivated to utilize any of the well-known complexing agents routinely utilized in aqueous nasal formulations (e.g. EDTA, sodium edetate, citric acid, etc.). An ordinary skilled artisan would have had a reasonable expectation of success, because the addition of complexing agents to aqueous formulations (e.g. nasally administrable aqueous suspensions) is conventional in the art. Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because the combined teachings of the prior art is fairly suggestive of the claimed invention.

Response to Arguments

Appellant's arguments filed 6/29/10 have been fully considered but they are not persuasive. Appellants have traversed the instant rejection by presenting the same and/or similar arguments as were rebutted in the previous rejection. Thus, the Office's rebuttal arguments are herein incorporated by reference. The rejection is considered to remain proper and is maintained.

(C) Claims 75-76 are rejected under 35 U.S.C. 103(a) as being unpatentable over FLONASE® from the online Physician's Desk Reference (PDR®), as evidenced by the 1999-2000 Drug Information Handbook (Lacy, C.; Armstrong, L. L.; Armstrong, L. L.; Goldman, M. P.; Lance, L. L., Lexi-Comp, Inc.: Cleveland, 1999, pp. 445-446) in view of Bernini et al. (U.S. Patent No. 6,464,958), Harris (WO 99/18971) (IDS reference) and Osbakken et al. (US 2002/0061281), as applied to claims 1, 4-6, 10-13, 22-25, 27-30, and 35 above, and further in view of Walker ("Management of allergic rhinitis", *Nursing Times,* 2003, *99(23)*, Abstract) and Hamuy et al.("Topical antiviral agents for herpes simplex virus infections," *Drugs Today*, 1998, *34(12)*, Abstract Only).

Appellant Claims

Appellant claims a formulation as described above in the instant application that additionally comprises a therapeutic amount of an antiviral agent selected from a group consisting essentially of acyclovir, famciclovir, valacyclovir, edoxudine, ganciclovir, foscarnet, cidovir (vistide), vitrasert, and formivirsen, and in some embodiments further comprises a complexing agent (e.g. sodium edetate).

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

The teachings of FLONASE, the PDR®, the DIH, Bernini, Harris, and Osbakken are set forth above.

Walker teaches that viral and bacterial infection is the commonest acute cause of symptoms of allergic rhinitis (abstract).

Hamuy identifies several antiviral agents that have been used successfully to treat herpes simplex virus, including cidofovir, edoxudine, and penciclovir (abstract).

Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)

FLONASE® lacks the teaching of compositions comprising an antiviral agent and an antibacterial agent. The antibacterial agent deficiency is cured by the teachings of Osbakken (see Table 1). The antiviral agent deficiency is cured by the teachings of Walker and Hamuy, which have been provided as supporting documents to demonstrate that viral infections are art-recognized to play a role in the etiology of rhinitis (Walker) and that cidofovir and edoxudine are well-known anti-viral agents (Hamuy).

Finding of Prima Facie Obviousness Rational and Motivation
(MPEP §2142-2143)

It would have been prima facie obvious to an ordinary skilled artisan at the time of the instant invention to modify the FLONASE®/Bernini/Osbakken compositions to further comprise a known antiviral agent, such as cidofovir or edoxudine, because viral infections are known to play a role in the etiology of allergic rhinitis and cidofovir, edoxudine, acyclovir, ganiciclovir, foscarnet, and formivirsen are well-known antiviral agents. An ordinary skilled artisan would have had a reasonable expectation of success upon addition of a known antiviral agent, because viruses are known to play a role in the cause of acute allergic rhinitis and both cidofovir and edoxudine are known anti-viral agents. Regarding the particle size distributions recited in Appellant's claims, these have been addressed above in the previous rejections under 35 USC

§103(a) and the relevant reasoning is incorporated herein by reference. Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because the combined teachings of the prior art is fairly suggestive of the claimed invention.

(10) Response to Argument

(A) Appellant traverses the rejection of claims 1, 4-6, 10-13, 22-25, 27-30, 35, and 77 under 35 U.S.C. 103(a) as being unpatentable over FLONASE® from the online PDR®, as evidenced by the 1999-2000 Drug Information Handbook (Lexi-Comp, Inc.: Cleveland, 1999, pp. 445-446) in view of Bernini et al. (U.S. Patent No. 6,464,958), Harris (WO 99/18971) (IDS reference) and Osbakken et al. (US 2002/0061281) by arguing that (i) the particle size distribution (PSD) of the FLONASE® particles is markedly different from the PSD recited in Appellant's claims and allegedly there is no motivation in the art to modify the PSD of the FLONASE® particles; (ii) Appellants' claimed composition results in unexpected results compared to the FLONASE® product; (iii) the secondary references allegedly do not cure the deficiencies of the FLONASE® product or negate Appellant's allegedly surprising results attributed to the recited PSDs; and (iv) allegedly FLONASE®, Bernini, Harris, and Osbakken if considered alone or in combination fail to teach, suggest, or render predictable the recited particle size distribution characterized by five distinct levels and allegedly showing unexpected results.

The Examiner respectfully disagrees with Appellant's traversal arguments. In response to Appellant's arguments against the references individually, one cannot show nonobviousness

by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Regarding (i) and, in part, (iii)-(iv), it is acknowledged that the "ChemImage" data demonstrates that the particle size distribution of the commercially available FLONASE® product is not identical with the particles size distribution recited in Appellant's claims. This fact does not overcome the instant rejection, at least because the instant rejection is based on an obviousness analysis and not an anticipation analysis. The fact that the FLONASE® product does not exhibit an identical PSD is insufficient alone to overcome the instant rejection. Moreover, the combined prior art provides ample motivation to the ordinary skilled artisan to modify the PSD of the FLONASE® product. For example, both Bernini and Harris establish that it is a conventional practice to optimize particle size and PSD of particulate pharmaceutical formulations intended for delivery to the lungs or nasal mucosa. Additionally, by using Bernini's particle size optimization techniques the ordinary skilled artisan could successfully sterilize the resulting aqueous composition using gamma radiation in lieu of using sterile filtration, wherein the sterilization of pharmaceutical formulations is desirable, especially when treating patients having a disease caused by a microbial infection (*e.g.* a fungal infection).

Bernini's teachings also provide the ordinary skilled artisan with guidance on how to change variables to control the resulting particle size distribution (*e.g.* by varying the processing times and/or cycles used). Consequently, the combined prior provides the ordinary skilled artisan with a reasonable expectation of predictably and successfully modifying the particle size

distribution of pharmaceutical products comprising suspended corticosteroid solid particles in an aqueous medium, such as in the modification of the FLONASE® product.

Regarding the combination of an antifungal agent with an anti-inflammatory, Osbakken's teachings clearly establish that both anti-fungals and anti-inflammatory steroids, like fluticasone, beclomethasone, or mometasone, are routinely used to treat fungal-induced rhinitis. The administration of an anti-fungal to treat fungal-induced rhinitis is obvious, because it would be reasonably and predictably expected to treat the underlying fungal infection causing the rhinitis. Similarly, the co-administration of an anti-inflammatory steroid, with the aforementioned anti-fungal would be reasonably and predictably expected to successfully treat the inflammation of the nasal mucosa caused by the underlying fungal infection and provide symptomatic relief to the subject in need of treatment. Regarding the suitable amounts of anti-fungals, anti-inflammatories, and if needed, anti-viral agents, these are all well known in the art (Osbakken, PDR, and the DIH). Thus, the ordinary skilled artisan would have had a reasonable expectation of predictably and successfully preparing an aqueous suspension formulation comprising an anti-fungal agent, anti-inflammatory steroid (*e.g.* fluticasone), and/or an antiviral agent, if needed, in combination with conventional pharmaceutical excipients. The rejection is maintained.

Regarding (ii) and, in part, (iii)-(iv), Appellant's data demonstrating alleged unexpected results are based on subjective data. Appellants' "quantified" subjective data was originally graphically presented in Figures 1-4 of copending application 10/414,682 which has since been incorporated into the disclosure of the instant application. The raw Total Nasal Symptom Scores (TNSS) (*i.e.* these are aggregate data) are subjective data assigned values by patients on an arbitrary scale of 0 to 3, where 0 means no symptoms and 3 means "severe symptoms present,"

and wherein these subjective data were manipulated using the ANOVA model. Due to the nature of the TNSS as subjective data one must take Appellant's calculation of "percent differences" between individual data points in Appellant's figures with a grain of salt. The calculation of a percent difference between data points based on a measured quantifiable property, such as density, is much different, and likely more reliable and reproducible, than in the instant case wherein the calculated "percent difference" between individual data points of Appellant's invented composition and the FLONASE product are based upon differences between subjective values from an arbitrary scale. Additionally, Appellant's invented composition TNSS data compared to the TNSS data for the FLONASE® product exhibit the same pattern of fluctuations over a period of 2-14 days; is of a similar magnitude, and in several instances is essentially the same (see, for example, data points at days 4 and 10 for Dey Fluticasone High and FLONASE® Low in Figure 1). The general differences depicted in the Figures are, in the Examiner's opinion, merely a difference of degree at best and not a difference of kind. A difference of degree is not sufficient to support patentability. Contrary to Appellant's statements, Appellant's results when taken as a whole and compared to the results exhibited by FLONASE® are not considered to demonstrate anything surprising or unexpected, as has been explained in previously. Thus, Appellant's formulations are not considered to exhibit unexpected or surprising results. Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because the combined teachings of the prior art is fairly suggestive of the claimed invention. The instant rejection is maintained. The Board of Patent Appeals and Interferences (BPAI) is respectfully requested to affirm the instant rejection.

(B) Appellant traverses the rejection of claims 71-74 under 35 U.S.C. 103(a) as being unpatentable over FLONASE® from the online PDR®) as evidenced by the 1999-2000 Drug Information Handbook (Lexi-Comp, Inc.: Cleveland, 1999, pp. 445-446) in view of Bernini et al. (U.S. Patent No. 6,464,958), Harris (WO 99/18971) (IDS reference) and Osbakken et al. (US 2002/0061281), as applied to claims 1, 4-6, 10-13, 22-25, 27-30, and 35 above, and further in view of Doi (U.S. Patent No. 6,368,616) and Meade (U.S. Patent No. 6,608,054) by reiterating the same arguments rebutted in section (A) above and arguing that Doi and Meade fail to cure the alleged deficiencies of FLONASE, Bernini, Harris, and Osbakken. The rebuttal of Appellant's traversal arguments from section (A) is herein incorporated by reference. Appellant's arguments are unpersuasive for the reasons set forth above and the rejection is maintained. The BPAI is respectfully requested to affirm the instant rejection.

(C) Appellant traverses the rejection of claims 75-76 under 35 U.S.C. 103(a) as being unpatentable over FLONASE® from the online PDR®) as evidenced by the 1999-2000 Drug Information Handbook (Lexi-Comp, Inc.: Cleveland, 1999, pp. 445-446) in view of Bernini et al. (U.S. Patent No. 6,464,958), Harris (WO 99/18971) (IDS reference) and Osbakken et al. (US 2002/0061281), as applied to claims 1, 4-6, 10-13, 22-25, 27-30, and 35 above, and further in view of Walker ("Management of allergic rhinitis", *Nursing Times,* 2003, *99(23)*, Abstract) and Hamuy et al.("Topical antiviral agents for herpes simplex virus infections," *Drugs Today*, 1998, *34(12)*, Abstract Only) by reiterating the same arguments rebutted in section (A) above and arguing that Doi and Meade fail to cure the alleged deficiencies of FLONASE, Bernini, Harris, and Osbakken. The rebuttal of Appellant's traversal arguments from section (A) is herein

incorporated by reference. Appellant's arguments are unpersuasive for the reasons set forth above and the rejection is maintained. The BPAI is respectfully requested to affirm the instant rejection.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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